EXHIBIT 1

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June 11, 2008

Mr. Douglas Ellsworth
District Director
New Jersey District Office
United States Food and Drug Administration
10 Waterview Boulevard
Parsippany, NJ 07054

RELEASE
REVIEWED: ~~SAD~~ C.O. 3/13/09 DATE

Re: Response to FDA 483 issued to Actavis Totowa on 05/20/2008

Dear Mr. Ellsworth:

We respectfully submit this letter and its enclosures in response to Form FDA 483 observations presented to Actavis Totowa LLC ("Actavis Totowa" or "The Company") on May 20, 2008. The underlying inspection at our Totowa, NJ facility was conducted from March 18, 2008 to May 20, 2008.

Before taking up the Form 483 observations, we believe it helpful to briefly review related background developments. Before issuance of the Form 483 observations we address here, Actavis Totowa advised FDA concerning the remedial and preventive actions we committed to take in order to secure and maintain compliance with current Good Manufacturing requirements ("cGMP"). We shall not reiterate all details of the undertakings previously described to the District Office in correspondence and conversations. However, we believe it provides context for our responses to specific Form 483 observations to refer to major elements of that overall compliance plan.

It is quite fair to say, as we related in our April 28, 2008 letter, that Actavis Totowa prides itself in maintenance of cGMP compliance by virtue of comprehensive and robust quality systems. Thus, we were surprised and chagrined, as the last inspection developed, by our failure to have secured the compliance we had sought and committed to establish at Actavis Totowa. In recognition of that situation, which we concede is largely reflected in the Form 483 observations listed below, we took the following actions:

- All product manufacturing and distribution was suspended.
- A highly qualified team of consultants from [redacted] was engaged to assist Actavis Totowa in a complete evaluation of all its quality systems and the Company's products. (b)(4)
- With respect to previously distributed product, [redacted] is conducting a thorough risk assessment pursuant to a protocol that has been provided to the agency on May 30, 2008. (b)(4)
- The Company has reduced the number of products in its portfolio and, thus, the number of batches that need to be supported by its quality system.
- Resumption of manufacturing will entail notice to FDA and be gradual and measured. The Company and [redacted] will conduct comprehensive assessments to determine whether manufacturing can be supported by pertinent qualifications and validations, and whether (b)(4)

procedures adequate for in-process, finished product, and post-marketing monitoring and controls are in place. Only then will a product be suitable for release and distribution. As may be appropriate, equipment may be requalified, and methods and processes revalidated.

- Until such time as the Company determines that the Company's product release systems are sufficiently robust and reliable, [redacted] will audit Company release decisions and must concur before product is distributed. (b)(4)
- Product currently in warehouses continues to be quarantined. Although the Company had concluded that certain batches were suitable for distribution based on its assessments and risk-based assessments by [redacted] and resumed limited distribution for a short period of time, it has suspended that distribution. There are no plans to resume distribution of previously manufactured product. (b)(4)
- As part of our restructuring and corrective action initiative, we shall adopt procedures that require that Actavis Inc. management be regularly informed concerning site Quality Systems and cGMP compliance.
- Actavis Totowa has filed reports with the agency on a regular basis to provide updated information. We shall continue to do so, with the minor modification that such updates will henceforth be monthly, rather than weekly to more efficiently capture material developments.

We have structured our response to observations by setting out each observation, in whole or in part, followed by our corresponding responses. We have concentrated on addressing the portions of the observations based upon specific events and facts described, and have not always responded to conclusory assertions selected from Turbo 483 options, which may fail to accurately capture or correspond with specific observed findings of the investigators.

Observation 1:

The responsibilities and procedures applicable to the quality control unit are not fully followed.

Specifically, The Quality Unit routinely failed to document, investigate and address product quality issues at the time of occurrence including in-process, finished product and stability out of specification analytical results. There is no assurance that the Quality Unit has the procedures, personnel, or systems to adequately evaluate the quality or validation status of the approximately 55 ANDA/NDA products and 25 non-application prescription products that they can currently manufacture and release to the market. The impact on finished product quality on the marketplace was not evaluated despite the confirmed out of specification results for at least 15 different marketed prescription products evaluated.

Response:

Actavis Totowa has committed itself to personnel and systems needed to address issues raised during the inspection and to ensure sustainable quality systems. As an initial step, we have replaced site leadership and are integrating the operations of the Totowa facilities more closely with Actavis Totowa's other solid oral dose facilities. Additionally, Actavis Totowa has restructured the Quality Unit, as outlined in our May 21 and 30 letters. Attachments A and B. Current organizational charts show at a glance changes in management of the site, and specifically changes in the Quality Unit. Addendum 2 of Attachment B contains organizational charts. The new (and interim) organizational structure at the

Actavis Totowa facility reflects hiring of qualified new personnel and the assignment to Actavis Totowa of personnel from our Elizabeth, NJ, Lincolnton, NC, and Baltimore, MD facilities. All new and transferred personnel have proven track records of managing compliant pharmaceutical operations.

Anthony Delicato, formerly the QA Director for our Elizabeth site, has been appointed QA Director for all NJ Solid Oral Dose facilities. Mr. Delicato and other personnel from Actavis sites at Elizabeth, NJ, Lincolnton, NC, and Baltimore, MD have significant experience in implementing corrective actions and achieving sustainable initiatives in compliance-challenged organizations.

Mr. Delicato's direct reports include [redacted], who is responsible for the release of product at both the Actavis Totowa and Elizabeth sites; [redacted] a new hire who is responsible for managing investigations and deviations, complaints and CAPA initiatives at both these sites; [redacted], who is responsible for facility and equipment qualification support (QA) and support of Compliance Remediation projects; [redacted] who is responsible for Quality Engineering and Annual Product Reviews for NJ SOD Operations; [redacted] who is responsible for the Documentation team for Totowa overseeing Change Control and Documentation Management; [redacted] who is responsible for Production Support of Manufacturing and Packaging at Little Falls and Taft sites; [redacted] who is responsible for the Elizabeth Documentation group, is assuming responsibility for Production Support activities at the site; and [redacted] and [redacted] who will maintain responsibility for site Compliance.

In addition, we are evaluating all procedures and systems for adequacy. These procedures and systems will be revised and modified as needed. Retraining of personnel on new and revised procedures and processes is being conducted. In addition to our efforts, experts from [redacted] started their assessments of the Quality Systems on June 9 and will start the assessment of the Quality Unit itself on June 16. We anticipate that their efforts will enable us to further enhance our systems and procedures. We will work with [redacted] to define any systems gaps and the corrective measures needed to address them. The effectiveness of the Quality Unit will be assessed and revisions to our interim organizational structure may be necessary to strengthen the organization.

The Company's 25 non-application prescription products have been permanently discontinued. Of the 55 ANDA/NDA products (114 products strengths), 40 different product strengths of 19 formulations have been identified for possible resumption of production. These reductions will ultimately decrease the overall volume of the plant by [redacted] thereby reducing the strain on the Quality Unit. Because resumption of manufacturing will be gradual, stress on the Quality system will continue to be alleviated for the foreseeable future, and its resources can grow at a pace commensurate with need.

Observation 2:

Drug products failing to meet established specifications and quality control criteria are not rejected.

Specifically,

a. *During the packaging of Digoxin Tablets 0.125 mg, lot# 70924A1, five double thick tablets were observed. Quality Assurance approved a 100% visual inspection of the [redacted] tablet lot which resulted in an additional 15 double thick tablets. Although Quality Assurance was aware of the "double thick" tablet finding, the batch was then released based on AQL sampling which included visual inspection of 1330 tablets. No additional thickness testing or analytical evaluation of the double thick tablets was conducted. No root cause was determined for the defect; however the lot was released to the market by the Quality Unit on 1/28/08 following the visual inspection.*

(b)(4)

There was no documented evaluation of the approximately [redacted] lots that remained on the market at the time of inspection.

b. *Pentazocine and Naloxone Hydrochlorides Tablets, USP, 50 mg (base)/0.5 mg (base) were manufactured with an overage of approximately [redacted] Naloxone Hydrochloride. The master batch record, "incorrectly corrected" the moisture content for the Naloxone HCL Dihydrate which led to the overage for batches manufactured from 9/8/05 until 3/25/08. Additionally, the laboratory practice was to dry the in-house standard for Naloxone HCL Dihydrate, however the method did not correct for drying the standard so the analysis did not reveal the overage. The Quality Assurance investigation was incomplete at the time of inspection despite the known manufacturing overage. There was no documented evaluation of the approximately [redacted] batches that remained on the market at the time of inspection.* (b)(4) (b)(4)

Response:

We have revised our practices and procedures for handling deviation investigations in production and Out of Specification (OOS) results in the laboratory. Relevant SOPs; 0033-10, "Investigation System," Attachment C and DOI QC-059-13, "Laboratory Investigations," Attachment D, now identify roles and responsibilities for the conduct and conclusion of investigations and encompass appropriate breadth, depth, root cause analysis, involvement of other batches and impact analysis of all products associated with a similar "systems" problem. The newly appointed management team will strictly enforce these new procedures. We are in the process of establishing a Material Review Board (MRB), which will ensure review on a multi-disciplined management level, with oversight by the Director of Quality Assurance. The MRB has two primary functions. First it is responsible for tracking progress of investigations to ensure closure within 30 calendar days. Second, as part of its review of investigation findings, product impact, deviation requirements, appropriate justification and product dispositions are discussed and evaluated. Based on this review actions are identified and decisions are made. The Director of Quality Assurance will escalate critical or major issues to next level management within the Quality Unit, when needed. The MRB SOP is in draft form and will be provided in a monthly report when completed.

In regard to specific examples:

a) When the five double thick tablets were found during packaging, an investigation into the incident was initiated. We note that the discovery of these tablets occurred because a packaging operator detected double thick tablets on the tablet counter.

Thereafter, given the obvious difference in tablet sizes, a 100% visual inspection of the lot was performed to determine whether there were any additional double-thick tablets. Fifteen (15) additional tablets were found and removed from the batch. An AQL evaluation performed by QA was satisfactory, and the batch was released. There was no evidence that double-thick tablets reached the market, from this or any other Digoxin batch, and no adverse drug experience reports attributable to such tablets had been submitted during the past five years prior to May 7, 2008, when Actavis Totowa initiated a recall of all lots of Digoxin Tablets 0.125 mg & 0.250 mg. This was a precautionary measure to address the Agency's concerns.

b) Actavis Totowa identified the overage issue during stability testing and subsequently filed a Field Alert. The root cause of the overage was determined to be a duplicate correction for moisture in the ingredient Naloxone Hydrochloride Dihydrate. All product lots were subsequently recalled.

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Observation 3:

There is a failure to thoroughly review the failure of a batch or any of its components to meet any of its specifications whether or not the batch has been already distributed.

Specifically, the following products do not meet finished product or stability specification throughout the products marketed expiry:

a. *Out of specification assay results for Codeine Phosphate at the 12-month (89.5%, 90.7%, avg. 90.1%, spec. [redacted]) and 18-month (86.0%, 85.9%, avg. 85.9%, spec. [redacted]), 25°C/60%RH stability stations were obtained on 8/21/07 and 1/16/08, respectively for Carisoprodol, Aspirin and Codeine Phosphate 200mg/325mg/16mg Tablets, lot# 60484A1, an annual stability lot. Four of 17 retention samples were also out of specification for assay of Codeine Phosphate or Carisoprodol for lot#s 51044A1, 60121A1, 61024A1 and 5136A1. Although QA investigation 07-042, (initiated 7/20/07 and approved 11/9/07), revealed a manufacturing problem resulting in variability of the tablet bilayers for lot# 70484A, (Acceptance Value 19.2% for Carisoprodol, spec. [redacted]), the QA investigations for the stability out of specification results were not completed. There was no evaluation of the approximately ten batches on the market at the time of inspections and no evaluation of other bilayer products.*

b. *An out of specification assay value for Phentermine HCL (112.0%, 106.6%, spec. [redacted]) was obtained on 7/25/07 at the 24-month 25°C/60% RH stability time point for Phentermine HCL Capsules, 30 mg, lot# 5436A1, an annual stability lot. QA Investigation 07-066 concludes, "[redacted]" A second stability out of specification assay result, (114.3%, 114.8%, spec. [redacted]), was obtained on 12/3/07 at the 24-month 25°C/60% RH stability time point for Phentermine HCL Capsules, 30 mg, lot#5704AQ. There was no evaluation of the approximately [redacted] batches on the market at the time of inspection.*

c. *Out of specification assay and impurity results were obtained on 11/13/07 for Hydrocodone Bitartrate and Homatropine Methylbromide Tablets 5mg/1.5mg, lot# 5683A1, at the 24-month 25°C/60% RH stability time point, (Homatropine Methylbromide assay results 64.2%, 74.1%, spec. [redacted] Homatropine MBr impurity result: 1.0087%, spec. [redacted] unknown impurity 2.1089%, spec. [redacted]. Out of specification impurity results were also obtained on 12/26/07 during the testing of Hydrocodone Bitartrate and Homatropine Methylbromide Tablets 5mg/1.5mg, lot# 60437A1, an annual stability lot, at the 18-month 25°C/60% RH stability time point, (unknown impurities 0.9082%, 1.3246%, and 1.0546 spec. [redacted]. The Quality Assurance investigations were not completed and there was no evaluation of the [redacted] batches remaining on the market at the time of inspection.*

d. *Out of specification assay results were obtained on 12/4/07 for Amantadine Hydrochloride Capsules, USP, 100mg, lot# 60324A1, at the 18-month 25°C/60% RH stability time point, (assay results 96.3%, 91.9%, spec. [redacted]). They were confirmed by re-measurement and retest; however the laboratory and Quality Assurance investigations were not completed and approved. No evaluation of the [redacted] batches remaining on the market had been made at the time of inspection.*

e. *On 2/8/08 and 2/27/08, the 2006 and 2007 annual stability batches were out of specification for the known degradant [redacted] during the testing of Guanfacine Tablets, USP, 1mg and 2mg. The product has a 24 month expiry for both strengths. There was no completed QA investigation and no evaluation of the approximately [redacted] batches of 1 mg and 8 batches of 2 mg Guanfacine Tablets, USP that were on the market at the time of inspection.*

Packaged stability lot number (package size)	Strength	[redacted] (b)(4)	Specification (%)	Stability Station 25°C/60% RH	Date of OOS
60956A2 (100's)	2mg	1.51, 1.52 avg.1.51	[redacted] (b)(4)	15 months	2/27/08
60126A2 (100's)	1mg	2.05, 2.06 avg. 2.05	[redacted] (b)(4)	24 months	2/27/08
60126AQ (500's)	1mg	1.60, 1.60 avg. 1.60	[redacted] (b)(4)	24 months	2/27/08
70012A2 (100's)	1mg	1.68, 1.68 avg. 1.68	[redacted] (b)(4)	12 months	2/8/08
70012A1 (500's)	1mg	1.63, 1.62 avg. 1.62	[redacted] (b)(4)	12 months	2/8/08

f. *On 1/4/08, an out of specification stability result was received for the known degradation product,* (b)(4) [redacted], *during the testing of Mirtazipine Orally Disintegrating Tablets, 15 mg Lot 60794A1 at the 15-month 25°C/60% RH stability time point (result 0.54%* [redacted] *spec.* (b)(4) (b)(4) [redacted]. *On 2/26/08, a second set of out of specification results fro* [redacted] *was obtained* (b)(4) *during the testing of Mirtazipine Orally Disintegrating Tablets, 15 mg and 30 mg stability lot#s: 70279A1 (15 mg 9-month) (result 0.56%* [redacted]*; 70420A2 (15 mg 6-month) (result 0.57%* (b)(4) (b)(4) [redacted]*, and 70421A1 (30 mg 6-month) (result 0.55%* [redacted]*. There was no completed QA* (b)(4) *investigation and no evaluation of the approximately* [redacted] *batches of 15mg and* [redacted] *batches of 30mg* (b)(4) *Mirtazapine Orally Disintegrating Tablets remaining on the market at the time of inspection.*

g. *Out of specification results for a known impurity,* [redacted] *(2.79%, 2.81%, spec.* [redacted] (b)(4) (b)(4) [redacted] *were obtained for Glyburide (micronized) Tablets, 1.5mg, lot#60164A1 at the 18-month 25°C/60% RH stability time point on 10/3/07. The Quality Assurance Director in QA investigation 07-081, indicated that the only other batch on the market, 70200A1, (a stability batch), is* (b)(4) *"*[redacted]*" however; in the same report, it notes, "*[redacted] (b)(4) (b)(4) [redacted]*" Out of specification stability results for the known impurity,* (b)(4) [redacted] *(2.15% and 2.13%, spec.* [redacted]*, were again obtained on 3/26/08 for* (b)(4) *Glyburide (micronized) Tablets, 3.0mg, lot# 60170A1 and 60170AQ, respectively at the 24-month 25°C/60% RH stability time point. The Quality Assurance investigation remains incomplete. The impact of the out of specification stability results on the approximately* [redacted] *batches on the market at* (b)(4) *the time of inspection (*[redacted] *of 1.5mg and* [redacted] *of 3.0mg) was not evaluated.*

h. *Out of specification assay results were obtained for Chlordiazepoxide (assay 89.6%, 89.2%,* (b)(4) *spec.* [redacted] *for Chlordiazepoxide and Clidinium Bromide Capsules 5mg/2.5mg, lot# 5553A3 (100's) on 8/3/07 at the 24-month 25°C/60% RH stability time point. The lot has a 36 month expiry. A degradant was observed during assay testing but was not quantified. There are* (b)(4) [redacted] *A retention sample that was not maintained at 25°C/60% RH was used to retest the batch and was in specification, however the Quality Unit approved a protocol to test additional retention samples at expiry on10/10/07, which resulted in three additional out of specification assay result for Chlordiazepoxide at 36 months; (lot# 4753A3, assay avg. 89.5%; lot# 5262A3, assay avg. 88.9%; and lot# 5146A2, assay avg. 89.8%; spec.* (b)(4) [redacted]*. Approximately* [redacted] *batches with 36 month expiry and* [redacted] *batches with 24 month* (b)(4) *expiry remained on the market at the time of inspection.*

i. *Out of specification (low) assay results for Folic Acid were obtained for the prescription vitamin Multiret Folic Tablets 500mg, lot# 70607A1 (blister pack) at the 3-month, 25°C/60% RH stability time point on 1/8/08 (assay 87.3%, 87.2%, avg. 87.2%, spec.* [redacted]*. Out of* (b)(4) *specification assay results for Folic Acid were also obtained for lot# 70065A1 (blister pack) at the 12-month, 25°C/60% RH stability time point on 2/26/08 (assay80.1%, 78.0%, avg. 79.1%, spec.* (b)(4) [redacted] *There was no completed QA investigation and no evaluation of the* (b)(4) *approximately* [redacted] *batches on the market at the time of inspection.*

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j. *Out of specification (high) assay results for Thiamin Mononitrate were obtained for the pediatric prescription vitamin Multi Vita Bets with 1.0mg Fluoride and Iron Chewable Tablets, lot# 70602A1 (100's) at the 3-month, 25°C/60% RH stability time point on 11/22/08 (assay160.6%, 165.6%, avg. 163.1%, spec.* [redacted] *. Investigation OOSN# 07-155 revealed that a calculation error in the analytical method occurred in which test results were calculated and reported as Thiamin Mononitrate; however the label claim was for Thiamin. Recalculation resulted in assay results within specification for stability batch 70602A1. Recalculations were not conducted until approximately 2 months later for five formulations of Multi Vita Bets Thiamin to evaluate the impact of the error. Four finished product lots, (Multi Vita Bets, 0.5mg F and Fe Chewable Tablets, lot# 60642A, 61093A, Multi Vita Bets, with 1.0mg F Tablets 60345A, Multi Vita Bets with 0.25mg F Chewable Tablets 60337A), and four stability lots, (Multi Vita Bets with 0.25mg F Chewable Tablets 60226AQ, Multi Vita Bets with 0.5mg F Tablets 60259AQ, Multi Vita Bets, with 1.0mg F Tablets 60205A1, 60205A2) were out of specification (low) by recalculation for Thiamin. The remaining 10 prescription vitamins containing Thiamin had not been evaluated at the time of inspection.* (b)(4)

k. *Out of specification (low) assay results for Acetaminophen and Dichloralphenazone were obtained for Amidrine Capsules, lot# 50638A1, an annual stability lot, at the 24-month, 25°C/60% RH stability time point, (Acetaminophen assay81.8%, 86.6%, avg. 84.2%, spec.* [redacted]*;* (b)(4) *Dichloralphenazone assay 82.6%, 85.7%, avg. 84.1%, avg. 84.1%, spec.* [redacted]*. In a* (b)(4) *repeat test conducted by a second analyst, the Acetaminophen and Dichloralphenazone results were within specification but "borderline"; however the assay results of the third active ingredient, Isometheptene Mucate were out of specification (Isometheptene Mucate assay108.4%, 110.2%, 107.7%, 108.9%, avg. 108.8%, spec.* [redacted]*. There was no completed QA investigation* (b)(4) *and no evaluation of the approximately* [redacted] *lots on the market.*

(b)(4)

Response:

We have revised our procedures for handling stability failures. As noted in our response to the preceding observation, these SOPs (SOP 0033-10, "Investigation System," and DOI QC-0059-13, "Laboratory Investigations") now identify roles and responsibilities for the conduct and conclusion of investigations and encompass appropriate breadth, depth, root cause analysis, implications for other batches, and impact analyses of all products with a similar "systems" problem. DOI QC-0059 requires that QA and QC be immediately notified of an event requiring an investigation. QA will assign investigation numbers and investigations now will be tracked by QA to ensure that practices are timely and consistent. The newly appointed management team will strictly enforce these new practices and procedures. As noted above, our newly constituted MRB will provide a senior, multi-disciplined review body to resolve issues.

Investigations for each of the above referenced stability failures have either been completed or are being conducted. The company and [redacted] assessments of distributed products will include full (b)(4) review of stability data. These investigations and reviews are targeted to be completed by July 11, 2008.

Finally, we observe that all lots of the products cited above have been recalled. There are no immediate plans to reintroduce these products into the market.

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Observation 4:

Determinations of conformance to appropriate written specifications for acceptance are deficient for in-process materials.

Specifically,

a. *Although three out of specification results were obtained for blend uniformity at the [redacted]" sample location for Digoxin Tablets 0.125 mg, lot#s 70148A (OOSN07-016), 70207A (OOSN07-022), and 70770A (OOSN07-116) on 2/20/07, 3/14/07 and 9/29/07; no manufacturing investigations were conducted. Additional samples were used to retest the blend and were reported. Lot# 70207A1 was released on 6/7/07 and lot# 70770A1 was released on 11/30/07 by the Quality Unit. Lot# 70148A was not released due to atypical content uniformity results.* (b)(4)

b. *Out of specification in-process results were obtained for friability of start-up and compression composite samples for Methenamine Mandelate Tablets 1.0g, lot# 70662A on 10/12/07. Despite the in-process out of specification results the batch was released to the market on 2/5/08 by the Quality Unit.*

c. *Although approximately 5 products were "temporarily discontinued" due to blend and/or content uniformity issues, there was no scientific rationale provided for the change of in-process blend uniformity specifications from [redacted] RSD [redacted] to [redacted] RSD [redacted]* (b)(4)

d. *Out of specification in-process blend uniformity testing of Oxycodone Tablets, 15mg, lot# 70164A was obtained on 3/3/07 (RSD 5.3%, spec. [redacted]. Remeasurement confirmed the out of specification results (RSD 6.0%, spec. [redacted]. No manufacturing investigation was conducted. A repeat test using a second set of blend samples resulted in an RSD of 4.6%. The batch was completed and released on 4/7/07.* (b)(4)

Response:

We acknowledge the propriety of the observation on conformance to appropriate written procedures. To this end, and as previously discussed, we have revised our investigation procedures, restructured our Quality organization, retrained personnel, and will provide senior management safe-guards such as a Material Review Board, to assure that all OOS and deviation investigations are fully evaluated. OOS and deviation trends will be evaluated to identify issues and ensure that our corrective measures are effective. Regarding blend uniformity/friability failures, and as part of our sustainable compliance efforts, we are currently performing product assessments to evaluate the robustness of our manufacturing procedures. The outcome of these process assessments could trigger process revalidation studies that will incorporate stratified sampling as a regular validation tool to properly challenge and correlate the various stages of our manufacturing processes.

In regard to the specific examples:

a) The subsequent testing of this blend was performed on contingency samples. Contingency samples are taken with original samples to permit further evaluation in the event an issue arises; for example, contingency samples are tested if OOS results are obtained from initial blend samples. Our revised investigation procedure (Reference Attachment C, Appendix – V of SOP 0033-10, page 14) now includes a form that prompts QA investigation specialists to look at historical information and evaluate trends. This SOP requires review of prior investigations of the same product, and products potentially affected by the same type of incident.

b) Start-up friability results were not available from the QC laboratory prior to initiating compression. When the results from start-up and composite samples were reported, an investigation was conducted to evaluate further processing of the batch. The investigation determined that other in-process tests were in specification and did not negatively impact the quality of the batch.

Start-up and in-process friability testing is now to be performed by Manufacturing during batch production, and test results are to be made immediately available on the production floor. All start up requirements will be fulfilled before proceeding. We note finally that this product has been recalled for other reasons.

(b)(4) c) We previously received correspondence from the Agency asking us to adopt a blend content uniformity specification of [redacted] with a [redacted] In an effort to achieve consistency (b)(4) in respect to blend specifications, Actavis Totowa elected to adopt this specification for all products, at least to the extent possible. We now recognize that this specification may not be appropriate in some cases. Accordingly, we shall evaluate in-process blend data and specifications for each product to ensure that appropriate blend specifications are in place. These reviews will be performed during assessments of products that are candidates for resumed manufacturing. As these and new products are introduced, we will employ a stratified sampling approach to provide the data necessary for justifying these specification limits or revert back to the specifications in place prior to the change.

d) SOP 0033-10 states, QAIG shall assign the investigation to a lead investigator with the training and skills necessary to evaluate any process that generated the OOS result. Further, the SOP requires approval from QAIG for testing additional samples.

Observation 5:

Laboratory controls do not include the establishment of scientifically sound and appropriate specifications and test procedures designed to assure that components, in-process materials, and drug products conform to appropriate standards of identity, strength, quality and purity.

Specifically,

a. *Analytical method transfers for each method from the Little Falls, NJ Quality Control Laboratory to the new Totowa, NJ Quality Control Laboratory were not conducted. Only two types of analytical methods, HPLC and GC were used to support the analytical transfer of approximately [redacted] in-process, finished product and stability methods. There were no drying, and blend testing.* (b)(4)

b. *There is no analytical evaluation of impurities on stability for approximately 48 prescription drug products such as Oxycodone HCL Tablets, 5mg, Phenazopyridine HCL Tablets, 200mg, Methanamine Mandelate Tablets, USP 1g, and Prenatal Plus with 27 mg Iron Tablets to assure the strength, quality, and purity of the products throughout expiry.*

c. *A stability out-of-specification result for the Betaxolol Hydroxyethyl impurity (0.57%, spec.[redacted]) was observed during related substance testing of Betaxolol Tablets 10mg USP, lot# 60215A1 at the 24-month, 25°C/60% RH stability time point. The impurity [redacted]* (b)(4) (b)(4) *. Although it was determined that a new analytical method was required to adequately evaluate the product, the firm continued testing and releasing product to the marketplace. The Quality Assurance investigation was not completed at the time of the inspection and approximately [redacted] lots remained on the market.*

(b)(4)

d. *There is no assurance that all prescription vitamin products will maintain their labeled potency throughout expiry. Testing of all labeled ingredients on stability is not conducted. For example pediatric prescription multi-vitamins, Multi Vita-Bets with 0.25mg, 0.5mg, and 1.0mg Fluoride and Iron Chewable Tablets and pre-natal prescription vitamins, Prenatal Plus with 27mg Iron Tablets are not analyzed for Iron on stability.*

e. *Out of specification or suspect test results for low assay were reported for Amantadine HCL Capsules, 100mg in OOSN 06-015, dated 11/16/06, STR 07-065, dated 7/3/07, OOSN 07-168, dated 12/4/07 and OOSN 07-183, dated 12/29/07. OOSN 07-168 resulted in a confirmed 18-month out of specification stability result for assay; however the other investigations attributed the low assay results to "extraction issues" with the GC method and manufacturing investigations were not conducted. Although the need for method remediation has been documented for the GC extraction method for assay of Amantadine HCl Capsules, 100mg since 11/16/06, corrective actions have not been implemented. QA Investigation 08-003 for the out of specification stability result obtained 12/4/07 remained in draft at the time of inspection.*

Response:

a) On 05/07/2007, prior to the transfer of testing from the Quality Control Laboratory at the Little Falls facility to the Totowa facility a project plan (Attachment E: "Validation Project Plan for the Validation of Equipment and Systems at the QC Laboratory, Totowa") was prepared. On 08/29/2007, an assessment of equivalency testing (Attachment F: Analytical Transfer Assessment between the Quality Control Laboratories at Actavis Little Falls and Actavis Totowa) for the transfer of laboratory equipment and associated methods from Little Falls to Totowa was performed. The assessment identified three types of instrumentation/methodologies as requiring formal equivalency testing: high performance liquid chromatography (HPLC), gas chromatography (GC) and Laser Particle Size Analyzer [redacted] (b)(4) (Attachment G: Transfer Protocol and Report).

In response to observation 5a, on 05/28/2008, a retrospective assessment of the transfer of testing from the QC laboratory at Little Falls to Totowa was performed. It should be acknowledged that the same trained personnel, methods, equipment, and SOPs were in place at Little Falls and Totowa. In addition, a comparison of all instrument qualification at the two facilities established equivalency of instrument performances at Totowa facility (Attachment H: Calibration Comparison of Instrument Moved from Little Falls Facility to Totowa Facility). Within the latter framework, the assessment proceeded by dividing the laboratory methodology/instrumentation into three groups based on the proposed USP <1058>, "Analytical Instrument Qualification" as follows: a) analytical methods that do not require equipment, or if required, are basic in nature (*e.g.* magnetic stirrers), b) analytical methods that require minor equipment (*e.g.* balance), and c) analytical methods that require major equipment (*e.g.* HPLC).

The first group consisted of analytical methods/instruments such as acidity, alkalinity (litmus test), chloride content (precipitation), limit tests, clarity and color of solutions, crystallinity, specific gravity, fats and fixed oils, water soluble substances, ether soluble substances, and limit of non-volatile residue, among other tests, that require simple analytical equipment (*e.g.*, pycnometer, burettes, pipettes, *etc.*) or no equipment at all. No formal transfer of this group of analytical methods/instrumentation was necessary as the same laboratory personnel, practices, procedures and quality systems were in use at both facilities.

The second group of analytical methods/instruments is based on the usage of minor equipment (*e.g.* balances, potentiometric titrators, melting point apparatus, drying ovens for loss on drying testing, muffle furnaces, pH meters, refractometers, polarimeters, etc.). No formal transfer of this group of analytical methods was necessary as these instruments require qualification, calibration, and/or

verification of the operating ranges prior to use. In addition, the same laboratory personnel, practices, procedures and quality systems were in use at both facilities.

The third group of analytical methods/instruments includes analytical methods that require complicated equipment (*e.g.* dissolution apparatuses, HPLC, GC, atomic absorption and UV/Vis spectrometers, and fluorescence spectrometers, and laser particle size analyzers ([redacted]). The HPLC (b)(4) method testing was formally transferred and equivalency of testing was demonstrated under the Transfer Protocol and Report.

There was no official transfer or method equivalency testing for the methods that require use of dissolution apparatus, atomic absorption spectrometer, UV/Vis spectrometer, and fluorescence spectrometer testing. A comprehensive review of the associated instrument qualifications (IQ, OQ, and PQ) and calibrations, prior to and after the testing transfer occurred was performed. The review of data at both sites established equivalency of instrument performance at Little Falls and Totowa (Reference Attachment H). In addition, all analyses using the group three equipment methodologies require instrument performance verification such as a system suitability test, linear standard curve prior to sample analysis or USP calibrator tablets during the calibration of the dissolution equipment. The instrument performance verification ensures proper function of the equipment for the analytical testing and the same laboratory personnel, practices, procedures and quality systems were in use at both facilities, and therefore, the analytical results were not impacted by the analytical testing transfer.

Analytical methods that required particle size analysis using the laser particle size analyzer (b)(4) ([redacted]) were not transferred as this equipment was never present in the Little Falls facility. A new (b)(4) Laser Particle Size Analyzer ([redacted]) has been purchased for the Totowa facility and is currently undergoing qualification. GC methods that require direct injection were formally transferred and found to be equivalent. However, GC methods that require head space injections will necessitate the optimization of certain parameters as a different head space injector system will be used in the Totowa facility. As such, method verification will be performed prior to equipment usage.

In addition, test results for about (b)(4) [redacted] recent raw material lots generated at the Totowa facility were evaluated against the manufacturer's CoA results. The comparison of test results, covering the entire range of methodologies/instrumentation used at Totowa facility, further substantiates the reliability of testing at the Totowa facility (Attachment I: Raw Material Test Results - Comparison Tables).

Based on the additional assessments and data comparisons described above, equivalency of method testing at the Little Falls and Totowa facilities is established. In conclusion, based on the established equivalency of testing, the transfer of testing from the Little Falls to the Totowa facility has no impact on the product integrity/quality.

We view this as a laboratory move where we relocated people, methods, equipment and SOPs. In the event that we were to transfer methods to an alternate testing lab, we would follow the appropriate SOPs governing Method Transfers.

b) On May 19, 2008, Actavis Totowa decided to recall these 48 products based on method inadequacies. This was a pragmatic decision based on consideration of the amount of time needed to fully and accurately validate the methods necessary, and the consequent delay of product impact assessments for distributed lots.

c) As part of a preliminary method assessment for Betaxolol HCl Tablets, 10mg and 20mg, a comparison study of the current and proposed methods was performed and showed the current methods

(b)(4)
are not suitable to properly resolve the [redacted] known impurity peak from the solvent and placebo peaks. The current methods were found to be lacking in specificity, resulting in biased high impurity results. Attachment J Report # AR/JR/Betaxolol HCl/08-003. Actavis Totowa decided to develop and validate new, revised analytical methods. Method validation was completed on December 15, 2007. Attachment K Report # AR/FP/179180/RPT/RS. The new analytical methods were submitted to the governing application as a CBE-30 supplement on April 21, 2008. A minor deficiency letter requesting an enhancement of the system suitability requirement was issued on May 8, 2008. Actavis Totowa made appropriate changes to the analytical methods and submitted the revisions as a minor amendment to CBE-30 on June 4, 2008. Testing of the lot in question using the newly proposed method generated results that were well within specification. This demonstrates no negative impact to lots on the market. In light of our recent response to the deficiency letter we expect the new method to be effective on July 4, 2008.

d) Actavis Totowa initiated recalls of Multiret Folic Tablets on May 1, 2008, Multi Vita Bets on May 7, 2008, and all vitamin products on May 19, 2008. These actions were taken based upon consideration of the amount of time needed to fully and accurately validate the methods necessary, and the consequent delay of product impact assessments for distributed lots.

e) Actavis Totowa recalled Amantidine HCL Capsules on April 8, 2008 based upon the realization that considerable time would be needed to fully and accurately validate the methods necessary, thereby delaying product impact assessments for distributed lots.

Observation 6:

Investigations of an unexplained discrepancy and a failure of a batch or any of its components to meet any of its specifications did not extend to other batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy.

Specifically,

a. *Although QA investigation 07-093, dated 1/25/08, for double thick Digoxin Tablets 0.125mg, lot# 70924A1, did not establish a root cause for the defective tablets, the investigation was not expanded to evaluate all finished product lots or strengths of Digoxin Tablets. At the time of* (b)(4) *inspection there were approximately* [redacted] *lots of Digoxin Tablets 0.125mg and* [redacted] *lots of Digoxin Tablets 0.250mg on the market within expiry.* (b)(4)

b. *Although a tablet capping issue was identified for Oxycodone Tablets 5mg, lot# 70976A on 12/14/07 and was attributed to damaged punches and dies in QA investigation 07-102, the investigation did not evaluate the impact on other finished product lots or strengths. Subsequently, four additional lots of Oxycodone HCl Tablets exhibited tablet capping, (30mg) lot# 80095A1, 80096A1, 80174A1; (15mg) 80165A1. QA investigations 08-032 and 08-042 for capping of Oxycodone HCL Tablets conclude that no other batches are impacted. Manufacturing of all strengths of Oxycodone Tablets continued despite the capping issues.*

c. *Although an out of specification assay value (112.0%, 106.6%, spec.* [redacted] *was obtained at the 24-month, 25°C/60% RH stability time point for Phentermine HCL Capsules 30mg, lot# 5436A1 on 7/25/07, QA Investigation 07-066 concludes, "* [redacted] *" No root cause was identified and the investigation was not expanded to evaluate all finished product lots of Phentermine HCL Capsules. There are currently* [redacted] *lots of Phentermine HCL Capsules 30 mg on the market within expiry.* (b)(4) (b)(4) (b)(4) (b)(4)

d. *An error was identified in the formula calculation for Vitamin B1 (Thiamin) during the testing of the pediatric prescription vitamin, Multi Vita-Bets with 1.0 mg Fluoride, lot# 70602A1 at the 3-month*

25°C/60% RH stability time point on 11/22/07. It resulted in Thiamin assay values being reported approximately 20% higher than the actual assay value for all lots. Although a planned deviation was written 1/17/08 to correct the calculation for 5 different pediatric multi-vitamin prescription formulations containing Vitamin B1 (Thiamin), the QA investigation 08-021 was not initiated until 2/14/08 and only evaluated other lots of Multi Vita-Bets. The investigation failed to evaluate all products which contain Vitamin B1 (Thiamin). In addition, the QA investigation, which remains incomplete, describes the impact of the deviation on batches as " [redacted] (b)(4)

Response:

As discussed above we have revised our procedures for investigating OOS results and deviations. These SOPs now include forms that prompt investigators to consider the scope and potential impact of a problem including the identification of lots that could be adversely impacted. See Attachment C. Every investigation will consider the potential for involvement of other batches and require impact analysis of all product batches based on similar "systems" issues.

Observation 7:

An NDA-Field Alert Report was not submitted within three working days of receipt of information concerning a failure of one or more distributed batches of a drug to meet the specifications established for it in the application.

Specifically, field alert reports for the following products with confirmed stability out of specification results were not submitted within three working days of receipt of information:

a. *Phentermine HCL Capsules, 30mg (ANDA 40-227), 24-month 25°C/60% RH stability lot# 5436A1 (1000 count), was out of specification for high assay on 7/25/07. Phentermine HCL Capsules, 30 mg, 24-month 25°C/60% RH stability lot# 5704AQ (100 count), was out of specification for high assay on 11/30/07. The field alert report was filed 4/24/08, during the inspection.*
b. *Glyburide (Micronized) Tablets USP 1.5mg, (ANDA 75-947), 18-month, 25°C/60% RH stability lot# 60164A1 (100 count) was out of specification for a known impurity* [redacted] *on 10/3/07. The field alert report was filed 11/29/07.* (b)(4)
c. *Pentazocine and Naloxone Hydrochloride Tablets USP 50 mg/0.5mg, (ANDA 75-735) 9-month 25°C/60% RH stability lot# 70053A2 was out of specification for assay of Naloxone on 1/3/08. The field alert report was filed 2/3/08.*
d. *Mirtazapine Orally Disintegrating Tablets, 15mg, (ANDA 76-689), 15-month, 25°C/60% RH stability lot# 60794A1 (blister pack) was out of specification for a known degradant,* [redacted] *on 1/4/08. The field alert report was filed 4/4/08, during the inspection.* (b)(4)

Response:

To better assure consistent handling of OOS findings, we have strengthened SOP 0033-10, "Investigation System," and SOP QC-059-13, "Laboratory Investigations," both effective June 6, 2008. Reference Attachments C and D. They now require the newly formed Quality Assurance Investigations Group (QAIG), to evaluate actions to be taken for marketed batches, including Field Alert reporting. Any investigation must be initiated using a number assigned by QAIG, which thereafter can track the progress of these investigations.

The need to observe these SOPs and FDA requirements has been emphasized by new management to the site since February 2008, particularly, [redacted] Senior Manager of the Quality Assurance Investigations Group (QAIG) responsible for both Product Complaints and Investigations, and Anthony Delicato, who has assumed responsibility for Quality Assurance for NJ based SOD Operations, including the Actavis Totowa sites. (b)(4)

Formation of the QAIG group has improved our adherence to the requirement for filing Field Alert reports within three (3) working days. With respect to any issues identified after February 1, 2008, Actavis Totowa has filed fourteen (14) Field Alert reports. Of these, thirteen (13) were filed within three (3) working days; one (1) was filed on the fourth working day. This improved performance demonstrates our commitment to Field Alert report requirements.

Observation 8:

Written records are not always made of investigations into unexplained discrepancies and the failure of a batch or any of its components to meet specifications.

Specifically, Quality Assurance investigations are not documented at the time of occurrence and are not completed in a timely manner as required by SOP0033, Investigation of Deviations, dated 11/3/06. For example:

a. *There is no completed Quality Assurance investigation into the formulation and analytical method calculation errors that led to the overage of approximately 9% Naloxone for all batches of Pentazocine and Naloxone Hydrochlorides Tablets, USP, 50mg (base)/0.5mg (base) from 9/8/05 until 3/25/08. The out of specification 9-month assay results for lot# 70053A2 were obtained 1/3/08 and the formulation error began 9/8/05.*
b. *There was no completed Quality Assurance investigation into the two out of specification assay results for Carisoprodol, Aspirin and Codeine Phosphate Tablets, 200/325/16mg, lot# 60484A1, obtained 8/21/07 and 1/16/08, respectively for the 12 and 18-month stability time points. A bilayer manufacturing problem was identified 8/28/07 in OOSN 07-067 regarding an out of specification acceptance value for Carisoprodol, (19.2%, spec. [redacted], in Carisoprodol, Aspirin, and Codeine Phosphate Tablets, 200/325/16mg, lot# 70484A. Despite the known bilayer manufacturing problem and stability out of specification results, the Master Production Record for another bilayer product, Carisoprodol/Aspirin Tablets 200/325mg, was not placed on hold until 4/7/08, during the inspection.* (b)(4)
c. *No QA investigation was initiated following the confirmed stability out of specification known impurity, [redacted] at the 15-month time point for Mirtazapine Orally Disintegrating Tablets, 15mg, lot# 60794A1 on 1/4/08. Three additional out of specification stability results were obtained for lot#s 70279A1(9-month), 70420A2 (6-month), and Mirtazapine Orally Disintegrating Tablets, 30mg, lot# 70421A1 on 2/26/08 for the same known impurity. The QA investigration remained in draft during the inspection.* (b)(4)
d. *There was no completed Quality Assurance investigation into the 3-month and 12-month stability out of specification Folic Acid assay results for Multiret Folic 500 Tablets, lot#s 70607A1 and 70065A1 obtained 1/11/08 and 2/28/08, respectively.*
e. *There was no Quality Assurance investigation initiated for the discrepancy between the required stability time points as documented in the stability protocol versus the actual time points listed in the electronic stability program. The impact on other stability studies was not assessed. For example:*
    i. *The 9-month and 18-month stability stations were not originally included in the electronic stability program for Buspirone HCL Tablets, 5 mg, lot# 60502A2, 60502AQ, 70036A2,*

and 70036AQ. The time points were added on 10/30/07, approximately three weeks after the 9-month stability test date, 10/9/07, for lot# 60502A2.

ii. The 18-month stability station was not originally included in the electronic stability program for Drixoral Cold and Allergy ER Tablets, Tablets Lot # 70085A (7-DRT-1) blister pack.

f. No QA investigation was initiated when an operator observed grease visibly trickling off of the tablet press during the compression of Oxycodone HCL USP Tablets, 5 mg, lot# 70761A1 compressed from 9/18/07-9/23/07. QA investigation 07-073 was subsequently initiated for the lot on 10/3/07 due to the presence of black spots on the tablets, observed during the packaging operation.

Response:

This observation provides examples supporting our decision that a pronounced reduction in the company's product portfolio was needed to ease the burden on our QA function and better align its resources with the demands placed on them. Our procedures require that investigations be opened, that they be completed fully and timely, that they be documented appropriately, and that appropriate actions thereafter be taken. In too many instances, QA was burdened beyond its capacity to meet these SOP requirements. As we have advised the District Office, we are working to eliminate the existing backlog of investigations. Our plan is to be current by August 15, 2008. In other instances, QA was not notified of facts requiring an investigation. This is a behavioral situation that requires training, management support and overview, and enforcement.

Our remediation efforts will include, training that emphasizes documentation practices, recognition of deviations, notification to supervisors, investigation initiation and timely closure of investigations. Our new structure and resources give us confidence that the essential management support is available for these initiatives. We shall continue to report to FDA our progress in the coming months.

Observation 9:

Written production and process control procedures are not followed in the execution and process control functions and documented at the time of performance.

Specifically,

(b)(4) *a. SOP 0033, Revision 8, Investigation of Deviations, dated 11/3/06 requires completion of investigations within [redacted] working days. If an extension is needed, a memo to file describing the progress and the target completion date is required. Numerous Quality Assurance investigations remained open during the inspection including investigations of out of specification finished product and stability out of specification results such as Carisoprodol, Aspirin, and Codeine Phosphate Tablets, USP lot# 60484A1 initiated 9/4/07, Guanfacine Tablets 2mg, lot#s 5393A2 and 5393A1, initiated 12/11/07. Extension memos were routinely written and approved by the Quality Unit with no justification or description of the investigation progress or potential impact on other product on the market.*

b. SOP QC-059, Revision 12, Investigation of Out of Specification and Suspect Test Results, dated 7/26/07 does not clearly identify the steps to be taken or samples to be tested by each analyst in an investigation of out of specifications or suspect test results. Although solutions are suggested for re-measurement, there is no requirement to evaluate the original tablet grind material when testing a tablet product. Additionally, manufacturing investigations are not initiated at that time of retesting.

c. *SOP 0070, Revision 2, Filing Field Alert Report with the FDA, dated 10/31/07 requires the filing of a Field Alert within three working days after receipt of information (confirmed or unconfirmed) for such issues as stability failures or any other significant chemical, physical or other change in a distributed product. The procedure was not followed in that field alerts were not filed within three working days. For example: Phentermine HCL Capsules 30mg, lot# 5436A1 which was filed approximately 9 months after the out of specification stability result and Mirtazapine Orally Disintegrating Tablets, lot# 60794A1 which was filed approximately 3 months after the out of specification stability result.*

Response:

As noted above, we are aware of the need for timely action and believe changes we have discussed will permit us to meet the obligations set forth in SOPs.

a. SOP 0033 was revised to clarify the procedure provisions for extending investigations. Reference Attachment C, Appendix-III on page 12. If an investigation cannot be completed within the required [redacted] timeframe, a request for an extension must be made. This request must include any information relative to the investigation and a justification for the extension. When possible, an interim report should be written. Extensions should be granted only on an exception basis and should not be a routine matter. Requests for extensions will be evaluated and discussed at the Material Review Board (MRB). Extensions may only be approved by QAIG. QAIG staff will track investigations to ensure proper monitoring of the progress and timely closure.

(b)(4)

b. SOP QC-059 was revised to include specific steps to be taken when investigating an OOS result in the laboratory. Reference Attachment D. The SOP requires that an analyst use the original grind for retesting. As previously stated, laboratory investigations will be tracked by QAIG; therefore, QAIG will be able to monitor and approve the testing scheme and simultaneously initiate a review of the manufacturing steps to determine a possible cause.

c. As previously explained, our reconfigured QA unit must ensure the timely initiation of investigations, and monitor the progress and completeness of the investigation of OOS results, manufacturing deviations and consumer complaints. Since the formation of QAIG in February 2008, Field Alerts have been filed in a timely fashion. The additional controls in place with this new function as well as the formation of the MRB and new QA management, will ensure that Field Alert Reports are filed on time and that corrective actions are taken.

Observation 10:

Changes to written procedures are not reviewed and approved by the quality control unit.

Specifically,

Changes are not all captured within the formal change control system. Changes that are documented in Work Orders are not reviewed and approved by the Quality Unit. In addition, documentation of justification for changes within the change control system is required by SOP 0065, Change Control, but this justification is lacking in detail with respect to product quality. For example:

a. *Work Order Forms, which are not reviewed and approved by the Quality Unit, are issued when transferring equipment from one facility to another and when equipment is not functioning properly. For example:*

i. *The Quality Unit did not review and approve Work Order #1001 or Work Order #1039, issued on 12/27/07 and 2/12/08, respectively, to document the transfer of the [redacted] V-Blender; used for the production of Digoxin Tablets, from the Little Falls, NJ manufacturing facility to the Riverview, NJ manufacturing facility. No formal qualification was conducted following the movement of the blender from one site to another.* (b)(4)

ii. *The Quality Unit did not review and approve Work Order #1311, opened on 3/31/08, to document "[redacted]" A new sensor was ordered, but no evaluation for potential product impact was made. Vitaplex Tablets, batch# 80249A were manufactured on the equipment from 3/29/08-4/3/08. There is no notation of the work on the production record. Multiple formulations of pediatric prescription vitamins, Multi Vita Bets Tablets were also recently manufactured using the equipment.* (b)(4)

iii. *The Quality Unit did not review and approve Work Order #1354, opened on 4/4/08, to document "[redacted]" The main bearing was replaced due to this work order, but there was no evaluation for potential product impact. Cyclobenzaprine HCL Tablets, USP 5mg, batch# 80258A was coated 4/1/08-4/4/08 on this equipment and was used for such other products as Prenatal Plus with 27mg Iron Tablets, Dipyridamole Tablets, USP 75mg, and Mirtazapine Tablets, 30mg.* (b)(4)

b. *The justification for making changes within the change control system is not documented or is incomplete. For example:*

i. *No justification is included in Change Control Request Form CC-002299 regarding a change in chromatographic column in the analysis of Betaxolol Tablets, USP 10 mg and 20 mg. This change involved the replacement of the chromatographic column used for Assay and Impurity testing. The use of the new column with the existing analytical method resulted in co-elution of chromatographic peaks during impurity testing.*

ii. *Although Change Control Request Form C-0145, initiated on 3/17/08, was used to remove erroneous calculations which led to the overcharge of Naloxone in Pentazocine and Naloxone Hydrochlorides Tablets USP, 50mg/0.5mg, the justification for the change was not documented in the change control.*

iii. *Change Control Request Form C-01131 was initiated on 2/20/08 in order to change the container and closure for Hydrocodone Bitartrate and Homatropine Methylbromide Tablets 5mg/1.5mg to address out-of-specification impurity results on stability; however the change control does not include the justification for the proposed change.*

Response:

We are revising our procedures to ensure that all changes are reviewed at the appropriate supervisor level and have QA approval. Work orders for the Production facility will be evaluated to determine if Change Control or an investigation is required. These changes will ensure that the Quality unit has knowledge of proposed changes with potential product impact and the ability to evaluate changes before they are effected. The rationale for change control decisions will be documented. The Change Control Review Board will monitor the Change Control process for timeliness and efficiency. Appropriate procedures will be revised and provided with subsequent monthly updates.

Observation 11:

Drug product production and control records, are not reviewed and approved by the quality unit to determine compliance with all established, approved written procedures before a batch is released or distributed.

Specifically,

Investigations of Deviation Reports require a review by Quality Assurance, an approval by Regulatory Affairs/Quality Compliance and an approval of product disposition by the Head of Quality Assurance. On multiple occasions, these three signatories were completed by the same individual. For example:

a. *Investigation of Deviation Report #07-093, regarding double thick Digoxin Tablets 0.125 mg, lot #70924A1, was signed by the Director of Quality Assurance under the sections designated for Quality Assurance, Regulatory Affairs/Quality Compliance and the Head of Quality Assurance.*
b. *Investigation of Deviation Report #07-102, regarding capped tablets observed during the packaging of Oxycodone Hydrochloride Tablets, USP 5 mg, lot # 70976A, was signed by the Director of Quality Assurance under the sections designated for Quality Assurance, Regulatory Affairs/Quality Compliance and the Head of Quality Assurance.*
c. *Investigation of Deviation Report #07-059, regarding out of specification assay test results for Carisoprodol, Aspirin & Codeine Phosphate Tablets 200/325/16 mg, lot# 60484A1 at the 12-month 25°C/60% RH stability station was observed 8/21/08 and was signed by the Director of Quality Assurance on 3/7/08 under the sections designated for Quality Assurance and Regulatory Affairs/Quality Compliance. The section for Product Disposition to be signed by and the Head of Quality Assurance is currently not signed.*
d. *Investigation of Deviation Report #08-033, regarding discoloration of Multi Vita-Bets with 1.0 mg Fluoride Tablets, lot #60061A1 at the 24-month 25°C/60% RH stability station was signed by the Senior Manager Quality & Investigation on 3/25/08 under the sections designated for Quality Assurance, Regulatory Affairs/Quality Compliance and the Head of Quality Assurance.*

Response:

On June 6, 2008, we implemented SOP 0033-10, "Investigation System." This procedure specifies multiple levels of review and approval by separate and distinct functions. First, after the investigation is prepared by a Subject Matter Expert (SME) for a particular technical area, the investigation report is to be reviewed and approved by the Area Manager. Additional SMEs may be required to review and support an investigation. The investigation report then must be submitted to QAIG, where it is reviewed and approved. Finally, based on the scope and impact of the investigation, the investigation report may require the approval of the Director of Quality Assurance. In summary, three separate and distinct levels of approval from three different functions are required for approval.

Additionally, the site has established a Material Review Board (MRB). The MRB has two principal functions. First, it tracks the progress of each investigation to ensure completion within the established time frame. Second, a cross-functional MRB team reviews each investigation report for such things as product impact, deviation requirements, required justification, and product disposition. This process ensures that each deviation is thoroughly investigated by Quality Assurance, Quality Control, Operations, and Technical Services MRB representatives that can provide their expertise.

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After you and others at the District office have reviewed this submission, we would appreciate the opportunity to meet with you, respond to any questions you may have, and explain in more detail the quality improvement initiatives discussed in our response to the Form 483. To this end, we plan to call you next week to schedule a mutually agreeable time to meet and further discuss our response.

As a final note we ask that if a request for this FDA 483 is made through Freedom of Information the Agency provide a redacted copy of the observations along with our written response. Redacted copies will be provided for your convenience within the next week.

Sincerely,

Sigurdur Olafsson
Deputy CEO, Actavis Group
CEO, Actavis, Inc.

Phone: 973-993-4366
Fax: 973-993-4303

Attachments:
A – Correspondence of May 21, 2008
B – Correspondence of May 30, 2008
C – SOP 0033-10, "Investigation System"
D – SOP 0059-13, "Laboratory Investigations"
E – Validation Project Plan for the Validation of Equipment and Systems at the QC Laboratory, Totowa
F – Analytical Transfer Assessment Between The Quality Control Laboratories at Actavis Little Falls and Actavis Totowa
G – Transfer Protocol and Report
H – Calibration Comparison of Instrument Moved from Little Falls Facility to Totowa Facility
I – Raw Material Test Results - Comparison Tables
J – Report # AR/JR/Betaxolol HCl/08-003
K - Report # AR/FP/179180/RPT/RS

cc: Nancy Rolli, Director of Compliance, FDA
Andrew Ciaccia, Compliance Officer, FDA
Erin McCaffery, Investigator, FDA
Phyllis Lambridis, VP, US Quality & Compliance, Actavis
John LaRocca, VP Legal, Actavis
Jeffrey Rope, VP Totowa Operations, Actavis